REVIEW

Molecular genetic and clinical review of Ehlers–Danlos Type VIIA: implications for management by the plastic surgeon in a multidisciplinary setting

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Received 10 March 2008; accepted 15 November 2008

KEYWORDS
Ehlers–Danlos; VIIA; 7A; Wound healing; Complications; Soft-tissue reconstruction

Summary A syndrome now known as Ehlers–Danlos, comprising laxity and fragility of the skin associated with hypermobility of the large joints, was published in 1892 by Tschernogobow. Ehlers–Danlos type VIIA is an extremely rare form of the syndrome. While the UK-based Ehlers–Danlos Support Group * recommends that the surgical management of patients with Ehlers–Danlos VIIA should be carried out in conjunction with a plastic surgeon, there is nothing in the plastic surgery literature regarding this syndrome. The management of patients suffering from Ehlers–Danlos VIIA is highly complex, as a result of the breadth of genetic and phenotypic presentations, and resulting complications. We present a review of the literature regarding this syndrome and, in particular, the surgical problems that may be encountered. A case report outlining our experience of successfully managing this condition is also presented.

Ehlers–Danlos syndrome (EDS) comprises a group of genetically, biochemically and clinically diverse, heritable connective tissue disorders. The first comprehensive description of the syndrome comprising laxity and fragility of the skin associated with hypermobility of the large joints was published in 1892 by Tschernogobow, 1,2 and later both Ehlers and Danlos, 3–5 who were Danish and French
dermatologists, respectively, published their observations independently in the first decade of the 20th century. Subsequently, significant advances in modern biochemistry, DNA analysis and genetics have expanded the range of clinical phenotypes and pathogenesis. At least one in 5000 individuals worldwide suffer from EDS. Skin fragility, bleeding diathesis, excessive bruising, poor wound healing and atrophic scarring are common to all EDS subtypes, sometimes causing clinical complications relevant to plastic surgery. EDS type VIIA is extremely rare and only a handful of cases are known worldwide. The UK-based Ehlers–Danlos Support Group, which publishes extensive medical information for families of those suffering from EDS, recommends that the surgical management of patients with EDS type VIIA should be in conjunction with a plastic surgeon to optimise soft-tissue management. To our knowledge, there is nothing in the plastic surgery literature regarding the management of patients suffering from EDS type VIIA. We describe our experience of managing this case, make appropriate recommendations and discuss the management of EDS type VIIA in the context of other EDS type VII subtypes.

Case report

A 5-year-old Caucasian male with EDS type VIIA was referred to the department of plastic and reconstructive surgery from the spinal orthopaedic surgery service. He required spinal surgery and growing rod insertion to correct a severe progressive scoliosis. The spinal surgery team had consulted the Ehlers–Danlos Society, and its medical advisory team had advised management to continue in conjunction with plastic surgeons as a result of the known issues with skin and healing. A combined procedure (with orthopaedic and plastic surgeons) was performed to insert the growing rods at the University Hospital. During preparation of the patient in the anaesthetic room, the medial left thigh was unexpectedly lacerated by the application of an adhesive electrode. Intra-operatively, as expected, the patient had severe ligamentous laxity. A straight 8-cm incision was made to gain access to the thoracic vertebrae, and a curved 11-cm incision was used to gain access to the lumbar vertebrae. During the procedure, the patient developed ecchymoses with minimal skin pressure. Both the thigh laceration and the surgical incisions were closed in two layers using 4/0 Vicryl and 4/0 Moncryl by the plastic surgery team. The sutured incisions were supported with 2.54-cm Steri-strips and Mepore. During the procedure, the patient required 435 ml of colloids and 400 ml of crystalloids to maintain normovolaemia. Following the procedure, 340 ml of blood was administered in PICU due to postoperative anaemia and increasing base deficit. The 24-h postoperative stay in PICU was otherwise non-eventful, and the wound drained 120 ml in total. Intra-operative and postoperative antibiotics were administered. The patient gained a total of 5.5 cm height as a result of surgery.

In spite of an obvious degree of ligamentous laxity and skin fragility, the operative course was smooth, and no specific problems with haemostasis or skin closure were encountered.

Postoperatively, the Steri-strips and Mepore were retained for 4 weeks, and at 1-month outpatient follow-up, the wounds had healed. During this time, the skin had developed mild erythema from the adhesive dressing. Once the erythema had completely settled, 2.54-cm Micropore was placed longitudinally along the wound and changed daily for a further 2 months to support the wound edges. At 3-month follow-up, the wound was maturing satisfactorily and was pink and flat, with minimal stretching. The 2.54-cm Micropore was continued for a further month, at which point it was stopped by the parents due to skin irritation. At 6-month follow-up, both scars were pink and flat, with no evidence of hypertrophy. The lower scar was slightly stretched in the middle-to-lower two-thirds (see Figures 1–3).

Discussion

EDS comprises a broad group of connective tissue disorders which share defects in the synthesis and cross-linking of collagen. This results in an array of clinical manifestations, including fragile and hyperextensible skin, joint hypermobility, easy bruising and a propensity to scarring. Several classification systems for the EDS have been described, which has contributed to some discrepancies in classification and nomenclature. Between six and ten EDS subtypes have been described, variably classifying these types according to their molecular pathologies, clinical phenotypes and disease associations. Despite variation in terminology, each of these systems shares common descriptions of EDS type VII, the focus of

Figure 1 Postoperative photograph at 6 months.
The current discussion. EDS type VII is categorised by its molecular pathology and clinical presentation. Its clinical characteristics comprise early-onset congenital hip dislocation, ligament laxity, scoliosis, short stature and osteoporosis. EDS type VII has been termed the ‘arthrochalasis multiplex congenital’ type, with these phenotypes caused by defective type I collagen synthesis, a major structural protein in connective tissues.

The molecular changes in EDS type VII result in defects in the conversion of type I procollagen to collagen. Type I collagen is a protein containing two α1(I) chains and one α2(I) chain, which are coded by the genes COLIA1 and COLIA2. It is the most abundant structural protein in the mammalian body. Type I collagen is synthesised as a precursor protein, procollagen, which contains additional peptide sequences at both ends of the molecule which require proteolysis in order to produce functional collagen. EDS type VII results from failure of this enzymatic cleavage by the protease, ‘procollagen N-proteinase’. Other studies have also implicated differing molecular mechanisms in the pathogenesis of EDS type VII, including defects in the production of type V collagen and defects in the fibronectin extracellular matrix of fibroblasts.

While EDS type VII is caused by abnormal splicing of exon 6 in the COLIA1 or COLIA2 gene, it can be further classified according to its molecular basis into types VIIA, VIIIB and VIIIC. EDS type VIIA results from defects in the COLIA1 gene that encodes the proα2(I) chains of type 1 procollagen. EDS type VIIIB results from defects in the COLIA2 gene that encodes the proα2(I) chains of type 1 procollagen. EDS type VIIIC is due to mutations in the protease itself, which is generally the more severe phenotype. EDS types VIIA and VIIIB are often grouped together, known as the ‘arthrochalasia’ type of EDS, while EDS type VIIIC is known as the ‘dermatosparaxis’ type of EDS, as it is similar to its counterpart in animals. Of note, there are only a small number of cases of EDS type VII worldwide.

Arthrochalasia-type EDS disorders are autosomal dominant and present with bilateral hip dislocation, severe joint and ligamentous laxity and recurrent joint dislocations and subluxations. In addition, there are specific issues in the treatment of EDS type VIIA that are specific to the plastic surgeon.

Collagen, an essential component of skin and intimately involved in healing and scar formation, is impaired in EDS type VIIA. Skin is fragile and hyperextensible and has a specific diagnostic disorganisation of collagen fibril assembly, seen as misshapen collagen fibres on microscopy. (see Figure 4a and b). Even when they appear normal on electron microscopy, the collagen fibrils are uniformly smaller than normal. The fibril disorganisation and reduction in size and content of collagen have also been demonstrated on the routine microscopy of dermal skin biopsies in these patients.

Skin manifestations also include poor wound healing, ‘cigarette paper scarring’ (broad and thin scars), easy
bruising and a propensity to cutaneous bleeding. Unique cutaneous manifestations have also been reported in some series, including the prominent 'criss-cross patterning of the hands and feet' described in several patients, a significant amount of redundant skin and skin discolouration. While these effects have been widely reported in case series, the involvement of plastic surgeons and, in particular, guidelines for plastic surgical management, has not been reported.

In patients with EDS type VII, plastic surgical complications should be anticipated, and prepared for. These patients should be handled intra- and postoperatively with extreme care, due to skin fragility and bleeding tendencies. The pathological skin changes described previously mandate meticulous care in handling tissues and wound closure, and Steri-strips or retention sutures should be used to minimise skin tension. If non-absorbable skin sutures are used, they should be left in longer than normal. Although evidence for this care is notably lacking, our case report highlights the success of this approach, and, in view of the known pathophysiology of the condition, it would be unwise to treat wounds otherwise.

Due to the propensity of patients with EDS to bleed, it is sensible to cross-match adequate amounts of blood and rule out concomitant coagulopathies. Regional anaesthesia, arterial lines and central venous catheters should be avoided as much as possible, as these patients are at significantly increased risk of haematoma formation. If arterial blood sampling is necessary, a needle or catheter as small as possible should be used. While the vascular type of EDS is at greatest risk for bleeding complications, complications related to bleeding and vascular fragility are common to all types of EDS, and indeed the use of blood products and coagulation factors to correct bleeding tendencies in these patients have been described.

It has been postulated in the literature suggesting that Ehlers–Danlos patients have a 'resistance' to local anaesthetics. The effects of local anaesthetics are complex and depend on the individual chemical properties of the agent and a number of tissue factors. Studies have suggested that the lack of effectiveness of local anaesthetic solution is not due to rapid dispersal of solution in Ehlers–Danlos patients, as is often assumed.

While guidelines for management are lacking, the suggestions made are well supported by the underlying pathological changes in EDS type VII. Additional therapeutic targets in the healing of skin have also been suggested in both laboratory and clinical studies. Dexamethosone has been suggested as a means to improving the disordered organisation of fibronectin extracellular matrix in the fibroblasts of these patients as described earlier. In laboratory studies, it has been shown to correct the disordered fibroblasts, and, in clinical studies, it has been shown to do the same and to result in improved healing. While medical therapies are still experimental, the importance of treatment lies in the diagnosis of the syndrome and the adequate planning in consideration of potential complications.

In our case, the patient experienced only minor skin fragility and bruising intra-operatively, with excellent wound healing and few or no problems with insertion of the orthopaedic rods. At 3-month follow-up, the scars had healed satisfactorily, following careful wound closure and the use of supportive measures for 3 months postoperatively. Our patient had a significant improvement in his quality of life, with improved posture and a height gain of 5.5 cm. Future planning to partially re-open his incisions to extend the ‘growing’ rods at about 18 months and a similar wound closure regimen with the combined input of orthopaedics and plastic surgery will be undertaken to optimise outcomes.

EDS Type VII is an extremely rare condition affecting the synthesis of type I collagen and affecting connective tissues throughout the body. Implications for the plastic surgeon include effects on skin healing and scarring and the propensity for bruising and bleeding complications. As such, we suggest the inclusion of plastic surgical input in the preoperative planning for any patient with EDS type VII undergoing surgery of any kind.

**Conflict of interest**

None.
Funding
None.

References


**SURGICAL TIP**

A simple method for fishing out the umbilicus in abdominoplasty surgery

Retrieving the umbilicus after abdominoplasty is, sometimes, not an easy task and may be embarrassing to the surgeon. We found that tying the umbilicus to a suture and bring the suture through the abdominal wall can exactly position it at the centre of the neoumbilicus before closing the abdominoplasty wound (Figure 1a). Subsequently, the umbilicus can be easily brought out by excising a small piece of skin around the stitch (Figure 1b) to be finally sutured into its new location. This will save time otherwise spent in fishing out the buried umbilicus which can prove difficult to the extent that it may inevitably lead to the undoing of the procedure so as to retrieve the umbilicus.

**Conflict of interest/funding**

None.

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doi:10.1016/j.bjps.2009.01.053